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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Ts'o et al.

Application No. 09/888,164

Art Unit: Unassigned

Examiner: Unassigned

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For: LIGANDS TO ENHANCE CELLULAR UPTAKE OF BIOMOLECULES

PENDING CLAIMS AFTER ENTRY OF PRELIMINARY AMENDMENT

1. A construct comprising a homogeneous conjugate of formula A-L-P, wherein

A represents a hepatic ligand that specifically binds to a hepatic receptor, thereby facilitating the entrance of said conjugate into cells having said receptor;

L represents a bifunctional linker that is covalently linked to A in a regiospecific manner to form A-L; A-L is covalently linked to P in a regiospecific manner to form A-L-P;

P represents a biologically stable oligomer that binds to a hepatic pathogen, wherein P is released from the conjugate following hydrolysis or reduction of at least one specific biochemical linkage, and contains internucleotide linkages resistant to enzymatic hydrolysis or biodegradation upon release from the conjugate.

2. The construct of claim 1, wherein said oligomer is an oligonucleotide, an oligonucleotide analog or an oligonucleoside.

4. The construct of claim 1, wherein said pathogen is a hepatic virus.

5. The construct of claim 1, wherein said pathogen is a liver parasite.

6. The construct of claim 4, wherein said hepatic virus is a hepatitis virus.

7. The construct of claim 6, wherein said hepatitis virus is hepatitis B virus.

8. The construct of claim 4, wherein said oligomer binds to a surface antigen of said hepatic virus.

9. The construct of claim 4, wherein said oligomer binds to a core antigen of said hepatic virus.

10. The construct of claim 4, wherein said oligomer binds to an encapsidation sequence of said hepatic virus.

11. The construct of claim 6, wherein said hepatitis virus is a hepatitis C virus.

12. The construct of claim 6, wherein said hepatitis virus is a hepatitis D virus.

13. The construct of claim 5, wherein said liver parasite is plasmodium for malaria.

14. The construct of claim 8, wherein said surface antigen is an S-gene antigen.

15. The construct of claim 9, wherein said core antigen is a C-gene antigen.

16. The construct of claim 7, wherein said oligomer binds to an RNA preS1 open reading frame sequence.

17. The construct of claim 6, wherein said oligomer comprises a sequence selected from the group consisting of GTTCTCCATGTTCAG (SEQ ID NO.: 27), TTTATAAGGGTCGATGTCCAT (SEQ ID NO.: 28), and AAAGCCACCCAAGGCA (SEQ ID NO.: 29).

18. The construct of claim 2, wherein said oligomer comprises deoxyribose methylphosphonate internucleotide linkages.

19. The construct of claim 2, wherein said oligomer comprises deoxyribose phosphorothioate internucleotide linkages.

20. The construct of claim 2, wherein said oligomer comprises phosphodiester linkages.

21. The construct of claim 2, wherein said oligomer comprises a combination of deoxyribose methylphosphonate/phosphorothioate internucleotide linkages.

22. The construct of claim 2, wherein said oligomer comprises a combination of deoxyribose methylphosphonate/phosphodiester internucleotide linkages.

23. The construct of claim 2, wherein said oligomer comprises deoxyribose phosphorothioate/phosphodiester internucleotide linkages.

24. The construct of claim 2, wherein said oligomer comprises 2′-O-methylribose methylphosphonate internucleotide linkages.

25. The construct of claim 2, wherein said oligomer comprises 2′-O-methylribose phosphorothioate internucleotide linkages.

26. The construct of claim 2, wherein said oligomer comprises 2′-O-methylribose phosphodiester internucleotide linkages.

27. The construct of claim 2, wherein said oligomer comprises a combination of 2′-O-methylribose methylphosphonate/2′-O-methylribose phosphodiester internucleotide linkages.

28. The construct of claim 2, wherein said oligomer comprises a combination of 2′-O-methylribose methylphosphonate/2′-O-methylribose phosphorothioate internucleotide linkages.

29. The construct of claim 2, wherein said oligomer comprises a combination of 2′-O-methylribose phosphorothioate/2′-O-methylribose phosphodiester internucleotide linkages.

64. A pharmaceutical composition comprising a construct according to claim 1 and at least one pharmaceutically acceptable excipient or carrier.

65. The pharmaceutical composition of claim 64 wherein said oligomer binds to a hepatitis virus.

66. The pharmaceutical composition of claim 65 wherein said hepatitis virus is HDV.

67. The pharmaceutical composition of claim 65 wherein said hepatitis virus is HCV.

68. The pharmaceutical composition of claim 65 wherein said hepatitis virus is HBV.

69. The pharmaceutical composition of claim 68 wherein said oligomer comprises a sequence selected from the group consisting of $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (SEQ ID NO.: 27), $^{5'}$TTTATAAGGGTCGATGTCCAT$^{3'}$ (SEQ ID NO.: 28), and $^{5'}$AAAGCCACCCAAGGCA$^{3'}$(SEQ ID NO.: 29).

70. The pharmaceutical composition of claim 68 wherein the A-L moiety of said construct is YEE(ahGalNAc)$_3$ - SMCC.

71. The pharmaceutical composition of claim 70 wherein said construct is selected from the group consisting of YEE(ahGalNAc)$_3$ – SMCC - $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (SEQ ID NO.: 27), YEE(ahGalNAc)$_3$ - SMCC - $^{5'}$TTTATAAGGGTCGATGTCCAT$^{3'}$ (SEQ ID NO.: 28), and YEE(ahGalNAc)$_3$ - SMCC- $^{5'}$AAAGCCACCCAAGGCA$^{3'}$ (SEQ ID NO.: 29).
Please add the following new claims:

72. The construct of claim 1, wherein the A-L moiety of said construct is YEE(ah-GalNAc)$_3$-SMCC.

73. The construct of claim 1, wherein said construct is selected from the group consisting of YEE(ahGalNAc)$_3$ – SMCC - $^{5'}$GTTCTCCATGTTCAG$^{3'}$ (SEQ ID NO.: 27), YEE(ahGalNAc)$_3$ - SMCC - $^{5'}$TTTATAAGGGTCGATGTCCAT$^{3'}$ (SEQ ID NO.: 28), and YEE(ahGalNAc)$_3$ - SMCC- $^{5'}$AAAGCCACCCAAGGCA$^{3'}$ (SEQ ID NO.: 29).